Technology Assessment Program

Office of Patient Care Services

UPDATED INFORMATION FOR VA TECHNOLOGY ASSESSMENT PROGRAM (VATAP) REPORTS

In June 2000, VATAP was relocated within the Veterans Health Administration from the Office of Research & Development to the Office of Patient Care Services. The following report was produced prior to the relocation of VATAP.

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Appendix 8

Systematic Review: PET as a Diagnostic Test in Alzheimer's Disease

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Appendix 8

Systematic Review: PET as a Diagnostic Test in Alzheimer's Disease

The final literature database searches for the systematic reviews were performed on September 10, 1996; the assessment represents peer-reviewed literature published and indexed as of that date.

This Appendix to the PET assessment report presents the results of the systematic review of PET as a diagnostic test for Alzheimer's disease. Alzheimer's disease and other neurologic and psychiatric conditions are significant presences in the PET literature, and predate studies of the use of PET for diagnosis of diseases in other organ systems. Maisey and Jeffrey (1991) attribute this emphasis to the high level of metabolic activity of the brain and to the design of early PET scanners to accommodate only the head.

PET allows the qualitative and quantitative evaluation of cerebral physiology, and the exploration of the biochemical bases for clinical diseases. Fluorodeoxyglucose (FDG) PET brain studies have been used for the many research and clinical purposes related to the central nervous system, including (Hoffman, et al., 1993):

- definition of the magnitude and distribution of normal local cerebral glucose metabolism, and the effects of age and sex on metabolism;
- localization of seizure onset in patients who have partial complex seizures and who are being considered for temporal lobectomy (FDA approved use of FDG);
- assessment of brain tumors, including the degree of malignancy at the time of diagnosis, persistent postoperative tumor, differentiation of high- from low-grade tumors and radiation necrosis from persistent tumor;
- evaluation of schizophrenia, affective disorders, obsessive-compulsive disorder;
- study of cerebral metabolism in cerebrovascular disease;
- definition of regions of changed glucose metabolism in various forms of dementia, including Alzheimer's disease, Pick's disease, and Huntington's disease.

I. BACKGROUND

A. Description

Alzheimer's disease (AD) is a progressive neurodegenerative disorder, and is the most common form of dementia. Dementia is defined by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) as "the decline in memory and other cognitive functions in comparison with the patient's previous level of function as determined by a history of decline in performance and by abnormalities noted from clinical examination and neuropsychological tests" (Morris, 1994). Dementia is a diagnosis based on behavior and cannot be determined by imaging studies or laboratory tests, although specific causes of dementia may be identified by these means. More than 55 illnesses, some nonprogressive, can cause dementia. AD, alone or in combination with other illnesses, accounts for approximately 70% of cases of dementia in industrialized countries (Geldmacher and Whitehouse, 1996).

In AD, intellectual ability, abstraction, judgment, memory, language, and finally motor functions deteriorate (Mazziotta, et al., 1992). Cerebral (brain) tissue damage is widespread and complex, with progressive loss of synaptic (intercellular) connections and cell death. Genetic linkages with a number of chromosomes, including 1, 14, 21 (early onset disease), or 19 (late onset), have been identified for familial forms of AD (FAD). However, the etiology of most forms of non-familial ("sporadic") AD remains unknown (Schorderet, 1995).

B. Epidemiology

AD is the most common cause of progressive intellectual failure in middle or late life, and is the fourth leading cause of death in the developed world (Duff and Hardy, 1994). The etiology of AD remains undefined; risk factors that have been tested in analytic epidemiology studies include family history, head trauma, aluminum exposure, and viruses. Findings on all of these potentially associated factors have been equivocal (Larson, et al., 1992).

The prevalence of AD rises steadily from late middle age in all populations that have been studied: studies using formal clinical criteria for AD (see sections on description, above, and diagnosis, below) from both Europe and the United States found rates per 100 population of 3.1 to 15.3 in individuals over 65 years of age, 4.1 to 6.1 in those over 75 years of age, and 7.1 to 47.2 in those over 85 (Rockwood and Stadnyk, 1994). AD patients have a median survival of eight to ten years after onset (range, 1 - 20 years) (Larson, et al., 1992). Over 2 million people in the United States are incapacitated by AD to the degree that they require assistance with daily living. Estimates of the cost of care for those in the United States with AD have ranged from $44 billion (Mazziotta, et al., 1992) to $100 billion (Post, 1994) per year.

As the proportion of elderly individuals in the United States increases, AD becomes an increasingly important public health concern. At present, there are more than 8 million veterans ages 65 and older (37% of the total veteran population). Improving the diagnosis and treatment of AD is a major goal of the Veterans Administration health care system (Respess, 1995).

C. Diagnosis

Much of the information in this section was taken from the chapter on dementia (McCormick and Larson, 1991) in the book *Diagnostic Strategies for Common Medical Problems*, published by the American College of Physicians. This book is intended to give practicing clinicians tools for the quantitative interpretation of clinical and diagnostic test information (i.e., tools for the evidence-based application of diagnostic tests).

In the diagnostic strategy for AD, the presence of dementia is first determined, and then its cause is established. Screening for dementia involves tests such as the Mini-Mental State Exam, which tests a broad range of cognitive functions. Once screening has documented the presence of dementia, causes other than AD are excluded. In some patients meeting the criteria for dementia, cognitive impairment is due to medication side effects, depression, other central nervous system diseases or metabolic abnormalities. Some of these may be treated, resulting in improved or stabilized cognitive function.

A definitive diagnosis of AD is based on a typical clinical picture and histopathologic findings in samples of brain tissue. The histopathologic hallmarks of AD are neuritic or senile plaques (large extracellular protein deposits) and neurofibrillary tangles (bundles of abnormal protein filaments inside nerve cells). Nerve cell damage and death is most severe in the region of the hippocampus (a deep-lying structure in the temporal lobe of the cerebral hemispheres that is involved in memory functions).

In the absence of histological confirmation of AD, patients are referred to as having a diagnosis of dementia of the Alzheimer type (DAT), rather than as having AD. Subsequent sections of this review will use the classifications “AD” and “DAT” literally: “AD” will refer to cases in which the disease has been definitively diagnosed by histopathology, while “DAT” will refer to cases to which clinical criteria only have been applied.

The prevalence of any cause of dementia varies among populations. Estimating pretest probability of disease requires consideration of multiple factors: the patient’s age and race, whether (and in what type of hospital and on which ward) the patient is hospitalized. Reviews of dementia prevalence have included the following data for the veteran inpatient population (McCormick and Larson, 1991):

Alzheimer’s disease, 49 - 70% of cases of dementia
multi infarct dementia, 7 - 22%
infection, 1 - 3%
metabolic condition, 2%
neoplasm, 1 - 5%
normal pressure hydrocephalus, 2 - 5%
subdural hematoma, 3%
depression, 3%
Huntington’s disease, 1%
Parkinson’s disease, 4%
Alcoholism, 3 - 8%
Other, 2%
(progressive supranuclear palsy, frontotemporal dementia, Pick’s disease, cortical basal degeneration)

Table 1 NINCDS-ADRDA criteria for clinical diagnosis of Alzheimer's disease

Diagnosis	Criteria	Features consistent with diagnosis	Features inconsistent with diagnosis
PROBABLE Alzheimer's disease	• dementia established • deficits in two or more areas of cognition • deterioration is progressive • no disturbance of consciousness • onset between ages 40 and 90, most often after age 65 • no other systemic disorder	• progressive deterioration of individual cognitive functions • impaired activities of daily living and altered patterns of behavior • family history of similar disorders • laboratory results of: - normal lumbar puncture - normal pattern or nonspecific changes in EEG - evidence of progressive cerebral atrophy on CT After exclusion of causes of dementia other than Alzheimer's disease: • plateaus in the course of disease • associated psychiatric symptoms, physical outbursts, sexual disorders, and/or weight loss • other neurologic abnormalities (including motor), especially with more advanced disease • seizures in advanced disease • CT normal for age	• sudden onset • focal neurologic findings • seizures or gait disturbances at the onset or very early in the course of the illness
POSSIBLE Alzheimer's disease	• dementia syndrome in the absence of other neurologic, psychiatric, or systemic disorders sufficient to cause dementia • diagnosis may be made in the presence of second systemic or brain disorder not thought to be the cause of the dementia • should be used in research studies when a single, gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause		
DEFINITE Alzheimer's disease	• clinical criteria for probable Alzheimer's disease and • histopathologic evidence obtained from a biopsy or autopsy		
Classification of Alzheimer's disease for research purposes	Should specify features that may differentiate subtypes of the disorder: • familial occurrence • onset before age 65 • presence of trisomy-21 • coexistence of other relevant conditions such as Parkinson's disease		

Adapted from McKhann, et al., 1989

Clues that conditions other than AD may be the primary cause of dementia have been codified in clinical diagnostic criteria, including those of the National Institute of Neurologic and Communication Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) (McKann, et al, 1984; Table 1). Diagnostic and Statistical Manual (DSM-IIIR) criteria are also used. Table 2, adopted from McCormick and Larson (1991) and Kukull, et al. (1990), lists the operating characteristics of screening tests and clinical criteria in the diagnosis of dementia and AD. The data in the table come from evaluations of the clinical criteria against the gold standard of histopathologic diagnosis.

Table 2 Tests for dementia and AD

Test		*Sensitivity (%)*	*Specificity (%)*	*Likelihood Ratio*	
				positive	*negative*
Screening for dementia	*MMSE*	87	82	4.8	0.16
Diagnosing AD in demented patients	*NINCDS/ADRDA criteria*	92	65	2.6	0.12
	DSM-IIIR	76	80	3.8	0.30

The information in Table 2 should be considered when interpreting the published evaluations of PET's diagnostic accuracy in AD. Kukull, et al. (1991), point out that investigators wishing to ensure that patients classified as AD are more likely to be AD should choose DSM criteria, while investigators wishing to include the greatest number of AD cases, seldom assigning a false-negative diagnosis, should choose NINCDS/ADRDA criteria. Gearing, et al. (1995) note that diagnostic accuracy has improved over time with the increasing use of formal clinical criteria and that in none of the first 106 autopsies in demented patients enrolled in the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) study was a potentially treatable disorder mistakenly diagnosed as AD using clinical criteria.

D. Treatment

No cure for AD is currently available; two drugs (tacrine and donepezil) that appear to modify the course of AD in some patients have been approved by the FDA. Pharmacotherapy is also used to treat some of the neuropsychiatric and behavioral disturbances associated with AD, and pharmacologic agents intended to affect AD cognitive dysfunction directly are under investigation. The conceptual framework for these treatments is that AD is a progressive degenerative dementia caused by the loss of neurons, synapses, and associated metabolic dysfunction. Therefore, treatment efforts are focused on the replacement or enhancement of the function of existing neurons (Whitehouse and Geldmacher, 1994).

Several neurotransmitter systems affected in AD may contribute to the cognitive dysfunction and provide the basis for neurotransmitter replacement therapy. Dysfunction of the cholinergic system in AD and evidence that this system is involved in human cognition have led to clinical trials of cholinergic agents. Tacrine and donepezil, cholinesterase inhibitors, are currently the only FDA-approved drugs for the treatment of AD. Tacrine has a modestly positive effect on cognitive and behavioral function in 30% to 50% of mild to moderately impaired AD patients (Davis, et al., 1992); the clinical significance of these effects has been questioned, and tacrine does not affect the course of

the disease (Growdon 1992; Crismon, 1994). Tacrine has significant side effects, including reversible liver damage and cholinergic adverse effects (nausea, vomiting, diarrhea, abdominal pain, dyspepsia) (Growdon, 1992; Wagstaff and McTavish, 1994; Whitehouse and Geldmacher, 1994). Donepezil does not appear to be associated with hepatotoxicity (Rogers, et al., 1996).

E. Rationale for PET in AD

The primary role of diagnostic testing has been differential diagnosis of AD from reversible or treatable diseases. These include dementia due to medication intoxication, infection, metabolic or nutritional disorders; benign brain tumors; normal pressure hydrocephalus; or multiple infarct dementia (MID) due to a series of small strokes (Kuhl, 1991).

As discussed above, the clinical diagnosis of DAT does not correspond to AD in 100% of cases; diagnosis early in the course of the disease can be particularly problematic (Hoffman, 1993). Initial studies into the use of PET in patients who met clinical criteria for DAT were based on the desire to improve diagnostic certainty and to provide information on the pathophysiologic basis of the disease. With the availability of tacrine and donepezil and the ongoing research into other drug therapies for AD, a renewed impetus for an accurate clinical diagnosis, including a diagnosis for the very early stages of dementia, has been noted (Morris, 1994).

Jobst, et al. (1994), discussing CT as a diagnostic test for AD, summarize the reasons to work toward increasing the accuracy of antemortem AD diagnosis. While treatment of AD is still at a rudimentary stage, accurate diagnosis is a prerequisite to the selection of defined cases for evaluation of therapies. There is also a need for precise epidemiologic and demographic knowledge about Alzheimer's disease and other dementias and for the best possible antemortem diagnosis so that patients and their families can be provided with clear information that enables them to organize their lives.

F. Special methodologic considerations in evaluating a diagnostic test for Alzheimer's disease

Accurate estimation of the characteristics of a diagnostic test depends on the test's comparison with a (hypothetically) 100% accurate "gold standard" test. When PET is used to diagnose or stage cancer, as in the other systematic reviews conducted for this assessment, its results are compared to those obtained by biopsy. Biopsy, while imperfect, generally offers a quite accurate estimate of the presence or absence of cancer. Clinical criteria have been shown to be less than optimally accurate when compared to biopsy or autopsy diagnosis of Alzheimer's disease, and the potential biases discussed below can be assumed to be operating in the studies of PET as a diagnostic test for DAT.

If the reference or gold standard test is significantly inaccurate, the estimates of the new test's characteristics will be biased. Since the results of the new test and the reference test are likely to be positively correlated (i.e., statistically dependent), this bias will result in higher estimates of sensitivity and specificity for the new test than would be the case if the test were compared with a true measure of disease status. In the rarer cases where the reference test and the new test have statistically independent results, results with the new test will be biased toward zero for both sensitivity and specificity (Phelps and Hutson, 1995).

Methods for correcting bias in estimates of a new test's accuracy compared to an inaccurate "gold standard" test have been developed. Some of the methods have focused on the assumption that the reference test and the new test have statistically independent results, and permit an algebraic correction under specific circumstances (e.g. the reference test has known sensitivity and specificity) (Begg, 1987). However, the assumption of statistical independence of the new and reference tests is usually quite implausible for most applications, since covariates of both test results (such as stage or severity of disease) will affect both tests simultaneously (Begg, 1987).

Other, recently developed methods are applicable when the two tests are either statistically dependent or independent (Phelps and Hutson, 1995). These methods require the research studies measuring the new test's accuracy to estimate a *probability* that each subject is abnormal with the gold standard process, rather than a binary (normal vs abnormal) measure. Phelps and Hutson provide an example of the application of these methods to the use of MRI for the diagnosis of multiple sclerosis (MS).

In the absence of studies specifically designed for use of the correction methods outlined above, Begg (1989) recommends that at least a subset of patients in each diagnostic accuracy study for a new test have been definitively diagnosed. The estimates obtained from studies where most patients have not been definitively diagnosed must be interpreted with reference to the imperfect standard.

Ideally, evaluation of the accuracy of a diagnostic test for AD should rely on data obtained from cohort studies in which the test is applied at intervals before death in patients with DAT, other forms of dementia, and in controls, and all subjects are followed to death and autopsy. Such studies have been performed for CT and SPECT (see below), but the MDRC Technology Assessment Program was unable to locate any published studies that had used similar methods to evaluate PET.

A cooperative group of European PET centers *is* currently conducting such a study, which incorporates a standardized neuropsychological test battery, standardized PET data analysis, and follow-up to autopsy with standardized neuropathologic criteria (Dr. K. Herholz, Max Planck Institut, Germany; personal communication, 1996). The study focuses on patients with NINCDS/ADRDA "possible" AD (i.e. the group of patients in whom there is the greatest uncertainty regarding diagnosis and for whom a more accurate test would most contribute to posttest certainty) and patients with other causes of dementia. Copies of the study protocol are available from the MDRC Technology Assessment Program.

G. Alternative neuroimaging technologies and other tests relevant to diagnosing AD

1. Neuroimaging technologies

Neuroimaging (i.e., CT) for cases of suspected AD is generally considered only after a systematic evaluation of a patient's mental status and history, and of information from reliable informants. Diagnostic criteria help to rule out other causes of dementia. Based on the prevalence figures for AD in the hospitalized veteran population cited above (approximately 50% to 70%), clinical criteria (likelihood ratio of 1.3 to 2.8 in the presence of a positive test result, from Table 2) give posttest probabilities of disease from 75% to 90%. The American College of Physicians (McCormick and Larson, 1991) recommends that CT be reserved for patients in whom there is a clinical suspicion of a focal or destructive central

nervous system lesion (i.e., patients whose neurological exam or clinical history is more suggestive of a focal central nervous system lesion than of AD or other causes of dementia such as Parkinson's disease).
Jobst, et al. (1994) confirm that the role of neuroimaging in AD has been to identify and exclude other intracerebral pathologies. The results of current work with both PET and other neuroimaging technologies suggest that neuroimaging may eventually play a more direct diagnostic role. Alternate neuroimaging technologies, both structural (CT and MRI) and functional (SPECT), have generated equivalent levels of research activity to that seen in support of PET as a diagnostic test for AD. These technologies are generally more widely available than PET, and if diagnostic accuracy were comparable, would be likely to be more widely used.

Neuroimaging alternatives that have been directly compared to PET in cross sectional studies using clinical criteria for DAT as the diagnostic standard include MRI, CT, and SPECT (Table 5). CT, SPECT, and the combination of CT and SPECT have been studied in cohorts of patients followed to autopsy (Jobst, et al., 1992 and 1994; Table 6); these studies use definitive diagnosis by histopathology as the gold standard, and provide estimates of sensitivity and specificity unbiased by the inaccuracies associated with clinical criteria. The studies in Table 6 also document diagnostic thinking efficacy: Jobst, et al., provide information allowing the calculation posttest probability of disease from likelihood ratios and age-specific pretest probabilities; and Van Gool, et al., document the incremental contribution of SPECT after careful clinical and laboratory examinations in mildly demented elderly patients.

The studies in Table 6 provide models that would benefit all evaluations of tests for AD. Their methodological strengths include:

- cohort design incorporating an exceptionally high (96%) rate of consent to autopsy [using methods documented by King, et al. (1993)] in AD cases, cases with other dementing conditions, and controls (Jobst, et al., 1992 and 1994);

- results are framed in clinically useful terms (providing age-related pretest probability of disease and likelihood ratios from which to calculate posttest probability of disease) (Jobst, et al., 1992 and 1994);

- the interrater reliability of the tests has been calculated (Jobst, et al., 1992 and 1994);

- control groups include both those without dementia and those with other dementias (Jobst, et al., 1992 and 1994; Van Gool, et al., 1995);

- since discrepancies among all the criteria sets used for histopathologic diagnosis of AD are well recognized (Jarvik, et al., 1995), all diagnoses are made with rigorous application of the same criteria set (Jobst, et al., 1992 and 1994);

- the incremental diagnostic certainty supplied by an additional test is defined (Van Gool, et al., 1995).

2. Other tests

Other diagnostic tests are also under development for AD. These include: presence of the ε4 allele for apolipoprotein E (Nalbantoglu, et al., 1994; Reiman, et al., 1996; National Institute on Aging/Alzheimer's disease, 1996); tau (microtubule associated)

protein in cerebrospinal fluid (Arai, et al., 1995); decreased ß-amyloid peptide$_{42}$ in cerebrospinal fluid (Motter, et al., 1995), and hypersensitivity of pupil responses to tropicamide (Scinto, et al., 1994). While the these tests and other tests are still under investigation, their potential use could have important implications for the role of more expensive and less widely available technologies such as PET.

H. Ethical considerations in testing for AD

Technical efficacy studies (Section VII) have used PET to identify metabolic changes in the brains of patients with early DAT; pre-symptomatic individuals at risk for familial AD have also participated in PET studies (Small, et al., 1995). Other means of identifying individuals at risk for AD, such as apo ε typing, are commercially available (National Institute on Aging/Alzheimer's Association Working Group, 1996).

The National Institute on Aging/Alzheimer's Association Working Group (1996) noted that genetic risk factor assessment applied to diseases, such as AD, that involve the interaction of several genes and environmental factors is complicated by uncertainties in predicting and diagnosing multifactorial disorders, and by the potentially far-reaching social, ethical, and medicolegal implications of disclosure of genotype results. Many of these uncertainties would complicate any test for early or preclinical AD.

Post (1994) summarized ethical issues in AD, some of which relate to early diagnosis:

- pre-emptive suicide may be considered by patients who have received a diagnosis of AD early in the course of the disease;
- early diagnosis, in the absence of interventions to modify risk or treat the disease, may be associated harms that outweigh its benefits;
- patients have a legal and ethical right to decide, while still competent, to use or reject technologies should they become incompetent
- independent living, driving, insurance, and jobs may be threatened by a diagnosis of AD.

II. RESULTS

Fifty-five articles were selected from MEDLINE and other database searches and from the bibliographies of initially retrieved articles as meeting the screening criteria. After review, 23 (42%) were found to meet inclusion criteria: 15 met the definition of technical efficacy (Fryback and Thornbury, 1991; *Appendix 2: Assessing Diagnostic Technologies*); 6 met (with the exception of the gold standard) the evidence-based criteria for studies of a single diagnostic test, and an additional 2 studies met the evidence-based criteria while comparing PET with other neuroimaging tests.

Technical efficacy studies are listed in Section VII, below; data abstraction tables for these studies are on file with the MDRC Technology Assessment Program. For this review, the definition of technical efficacy was expanded to include those not designed to assess diagnostic accuracy or not meeting the evidence-based criteria for diagnostic accuracy. These studies do provide information necessary to subsequent diagnostic efficacy studies (Table 4). The MDRC Technology

Assessment Program was unable to locate any published PET studies at higher levels of the Fryback and Thornbury diagnostic efficacy hierarchy.

The technical efficacy studies listed in Section VII compared patients with DAT to non-demented controls and tested the differences between groups with inferential statistics. Rapoport (1991) summarized some of the conclusions that had been drawn at that time regarding brain metabolism in DAT from the studies that met technical efficacy criteria for this review and from other studies that have appeared in the literature:

- reductions in resting state regional brain metabolism are roughly proportional to dementia severity;
- metabolic reductions are greater in association areas than in primary sensory and motor neocortical areas, and correlate with the distribution of neuropathology and cell loss postmortem;
- brain metabolic patterns in DAT patients are heterogeneous, belonging to at least four distinct metabolic groups that correspond to different patterns of cognitive and behavioral abnormalities;
- abnormal left/right asymmetries in mild DAT can retain their initial direction for extended periods, and may precede and predict the cognitive deficits that later appear;
- parietal association/frontal association metabolic ratios also retain their direction over time;
- although metabolically spared compared to the association cortices, the primary sensory cortices, basal ganglia, thalamus, and cerebellar hemispheres show metabolic declines over time with high resolution scanners.

Table 4 presents the diagnostic accuracy efficacy studies located by the MDRC Technology Assessment Program. Since these studies used cross sectional with controls design, posttest probability of disease can be calculated and the studies can also be classified at the diagnostic thinking efficacy level. Additional support for the ability of PET to accurately predict clinical classification of DAT is provided by Hoffman, et al. (1996), who found that FDG PET studies had high inter- and intra-rater reliability in distinguishing probable and possible AD from other potential causes of dementia and memory disturbance.

III. SUMMARY

Table 3 summarizes published findings on the diagnostic accuracy and diagnostic thinking efficacy of PET and its neuroimaging alternatives. The PET studies did not met evidence-based medicine criteria (since histopathologic diagnosis was not the gold standard) but otherwise fulfilled most requirements for good methodologic quality. Unique features of each test are noted, as are the comparison groups used in each study. PET results were not quantitatively pooled, as each published study used a different method for PET data analysis and accuracy results fell within relatively narrow ranges. Histopathology is recognized as the gold standard for diagnosing Alzheimer's disease; studies that evaluate PET against clinical criteria may overestimate accuracy.

Table 3 Diagnostic accuracy and diagnostic thinking efficacy of PET and its neuroimaging alternatives

Neuroimaging Test	Diagnostic Standard Used in Evaluation Studies		Characteristics
	Histopathology	*Clinical criteria*	
CT	x		Se = 94%; Sp = 93.5% (AD-specific orientation; AD vs normal controls and other dementias) *Jobst, et al., 1994*
SPECT	x		Se = 96%; Sp = 89% (AD vs normal controls and other dementias) *Jobst, et al., 1994*
		x	Sp = 89% • all probable AD, Se = 43% • probable AD < 80 years, Se = 56% • probable AD > 80 years, Se = 29% • SPECT contributed to 8% of final diagnoses *Van Gool, et al., 1995*
CT + SPECT	x		Se = 90%; Sp = 97% (AD vs normal controls and other dementias) *Jobst, et al., 1994*
PET		x	Se = 94.6; Sp = 97% ("robust ratio"; DAT vs normal controls) *Herholz, et al., 1993* Post test probability of disease, positive test = 90%; posttest probability, negative test = 10% in patients with pretest probability of disease = 50% (neural net; DAT vs normal controls) *Kippenhan, et al., 1994* Se = 94%; Sp = 79% (4 image patterns typical of DAT; DAT vs normal controls) *Salmon, et al., 1994* Se = 94%; Sp = 53% (4 image patterns typical of DAT; DAT vs non-DAT dementia controls) *Salmon, et al., 1994* Se = 94%; Sp = 99% (stereotactic surface projections; DAT vs non-DAT controls) *Burdette, et al., 1996*
PET vs CT		x	PET: Se = 97%; Sp = 84% (qualitative) CT: Se = 86%; Sp = 28% (cortical atrophy) (DAT vs normal controls) *Fazekas, et al., 1989*
PET vs MRI		x	PET: Se = 97%; Sp = 84% (qualitative) MRI: Se = 92%; Sp = 60% (ventricular atrophy) (DAT vs normal controls) *Fazekas, et al., 1989*
PET vs SPECT		x	PET: Se = 80%; Sp = 100% (typical functional pattern) SPECT: Se = 80%; Sp = 65% (typical functional pattern) (DAT vs normal controls and vascular dementia) *Mielke, et al., 1994*

Se = sensitivity; Sp = specificity

IV. DISCUSSION

The face value of PET's diagnostic accuracy in AD appears to be very good, and fairly equivalent across a variety of data analysis methods and scanning protocols (Table 3; Herholz, et al., 1993). However, PET has been evaluated against clinical criteria (an imperfect diagnostic standard) only. Since the factors that affect clinical criteria accuracy (e.g. severity of disease) also are likely to affect PET results, the published sensitivity and specificity figures may be overestimates. The discussion sections of these papers note that further studies comparing PET to definitive diagnosis by histopathology are necessary to confirm results; a large cooperative study in Europe using histopathology as the diagnostic standard is currently under way.

An additional source of bias may be attributable to the choice of clinical criteria in PET diagnostic accuracy studies. All used NINCDS/ADRDA criteria, which are associated with a higher rate of false positives and a lower likelihood ratio for a positive test (2.6) than are the DSM-III criteria (likelihood ratio = 3.8). If DMS-III criteria are applied in patients with a pretest probability of AD of 60% (the midpoint of the hospitalized veteran prevalence range), the posttest probability of AD is approximately 85%. NINCDS/ADRDA criteria yield an approximately 80% posttest probability of AD.

Finally, most of the cases in PET diagnostic accuracy studies had possible or probable AD according to NINCDS/ADRDA criteria. Few studies applied PET prospectively to large numbers of patients with other diagnoses (e.g., vascular dementia), which would be necessary to fully define the positive predictive value of PET as a diagnostic test.

The clinical importance of differences in clinical criteria accuracy and the additional accuracy attributable to PET [posttest probability of disease in the hospitalized veteran population with face value sensitivity and specificity from Herholz, et al. (1993) of > 99%] rests on changes in management or treatment decisions that follow test results. Recent studies indicate that as clinicians have gained experience in the application of clinical criteria their accuracy has increased, and that treatable causes of dementia are rarely missed. Since treatment options for AD itself are currently limited and use of clinical criteria appears to miss very few treatable causes of dementia, increased diagnostic accuracy may be needed primarily in research settings (epidemiologic studies and evaluations of potential therapies). The value of improved diagnostic information to patients and their families should not be dismissed; however, this value remains unquantified.

The accuracy and potential research utility of PET in AD should be viewed in the context of the accessibility and accuracy of other imaging technologies (Tables 5 and 6), and that of other tests that are currently available or under development. In studies directly comparing PET with standard CT, MRI, or SPECT using clinical criteria as the diagnostic standard, PET has superior characteristics (Table 5). On the other hand, AD-specific and relatively simple CT and SPECT methods have been tested in rigorously designed cohort studies in which demented patients (AD and other causes) and non-demented controls have been followed to death and definitive diagnosis; these studies indicated that CT and SPECT may have sensitivity and specificity close to that of PET (Table 6).

V. CONCLUSIONS: Clinical use of PET in Alzheimer's disease

As of September, 1996, the accuracy of FDG PET in diagnosing Alzheimer's disease had been demonstrated in 5 published studies that used a variety of methods to analyze PET data and to arrive at decisions about the presence or absence of disease. These studies compared PET to clinical criteria for dementia of the Alzheimer's type. While the clinical criteria are known to be somewhat inaccurate in diagnosing AD, compared to the gold standard of histopathologic diagnosis, careful application of the criteria does appear to identify most cases of treatable dementia.

The factors noted in the discussion section and the paragraph above argue that routine clinical application of PET as a diagnostic tool for AD should await the results of the ongoing European multicenter study that will evaluate PET's accuracy against the diagnostic standard of histopathology, as well as development of more effective treatments and risk modification interventions for AD. The multicenter study's results will allow more explicit comparisons among PET and more widely available tests that may have comparable accuracy. In the absence of effective treatments for Alzheimer's disease, an accurate diagnostic test may be needed primarily in the efficacy of treatment research setting.

Finally, the role of diagnostic tests in treatment efficacy research protocols may need refinement as subsets of Alzheimer's disease are defined by phenotypic or genetic markers. Nalbantoglu, et al. (1994) calculated the population attributable risk for the ε4 allele for apolipoprotein E at about 50%. This level of attributable risk suggests that late-onset AD consists of at least two disease entities with separate underlying causes or aggravating factors. Each of the disease entities may require different treatment strategies, and selection of patients for treatment may be based on molecular or genetic tests, rather than on anatomic or functional imaging studies. Small, et al. (1995) found that the ε4 allele is associated with reduced cerebral parietal metabolism and increased asymmetry in non-demented relatives at risk for probable AD. Measurement of glucose metabolism using PET could be a means of monitoring experimental treatment responses during early phases of AD.

Table 4 Summary of the literature: Diagnostic accuracy efficacy of FDG PET imaging in Alzheimer's disease

Notes: *Studies are listed in order of date of publication. Where substantial duplication in purpose of study, patients studied, and results in multiple studies from the same institution could be inferred, only the most recent, largest, most rigorously designed, or most comprehensive was included in the table. Studies reviewed but not included are listed under "References".*

All studies in this table used a cross sectional design with controls, and provided Level III evidence (see Table 2 for an explanation of levels of evidence).

In several studies in this table, images were interpreted without blinding of image readers to clinical diagnosis, or blinding was not noted. In these studies, however, PET data were analyzed quantitatively (often by automated processes) rather than visually (qualitatively), minimizing observer bias.

Study	*Subjects/Methods*	*Results/Comments*
Azari, et al., 1993 *NIA/NIH, NIMH/NIH, Washington State Mental Illness Research & Training Institute*	**Purpose** to investigate whether a multiple regression/discriminant analysis procedure would distinguish mildly/moderately demented patients with probable AD from controls **Cases** 19 mildly/moderately demented patients with NINCDS-ADRDA probable AD **Subject at risk** 1 subject at risk for familial AD with only delayed memory at time of study **Controls** 22 healthy age- and sex-matched controls **Methods** • PET scans parallel to IOM obtained • absolute and normalized GMR obtained for 65 ROIs and whole brain • analysis involved: - selection of 2 sets of regions as dependent variables (frontal/parietal association areas and 4 smaller ROIs) - stepwise multiple regression to identify best predictors - application of regression weights to control and AD data - application of discriminant analyses to determine the weighting of regression residuals to maximize differences between cases and controls - cross validation of discriminant functions using jackknife procedure • each subject classified as control or AD using a discriminant function • discriminant functions applied to subject at risk	**Estimated posttest probabilities of group membership:** • using statistical functions based on frontal/parietal region, 95% of AD cases and controls correctly classified • average probability of correct classification: - cases, 0.97 (0.78 - 1.00) - controls, 0.93 (0.53 - 1.00) **Cross validation of discriminant functions, frontal/parietal region:** • 89% of AD patients and 86% of controls correctly classified • average probability of correct classification: - cases , 0.90 (0.55 to 1.00) - controls, 095 (0.52 - 1.00) **Cross validation of discriminant functions, 4 smaller ROIs:** • 88% of AD patients and 81% of controls correctly classified • average probability of correct classification: - cases,1.00 - controls, 0.98 (0.83 - 1.00) **Application of discriminant functions to subject at risk:** • frontal/parietal: probability of classification as AD, 0.74; as control, 0.26 at first PET study; probabilities 0.84 and 0.16, respectively, at second PET study (1 year after first) • 4 smaller areas: first and second PET studies showed had probability of classifying subject as AD of 1.00 **Success of group separation** 2 discriminant functions separated groups (5 subjects misclassified) with less overlap than single, normalized glucose metabolic index. **Conclusion** This statistical approach may be useful for early detection of AD. **Study design limitation** no definitive diagnosis in any DAT subjects

Study	*Subjects/Methods*	*Results/Comments*
Herholz, et al., 1993 *Max Planck Institut, Cologne; Hospital San Raffaele, Milan; Université de Liège*	**Purpose** to assess whether a study protocol based on a robust ratio to assess the typical metabolic pattern of AD can yield comparable results in 3 different centers **Cases** 37 patients with NINCDS-ADRDA probable AD **Controls** 34 healthy subjects **Methods** • multiple PET slices parallel to CM line from cerebellum to ≥ 27 mm above basal ganglia • GMR calculated according to machine and software properties of each center • experienced physician performed examined images visually, with access to clinical information (analogous to clinical practice) • ROIs defined and GMRs calculated for regions most typically affected by AD (temporoparietal and frontal) • composite metabolic ratio representing typical pattern in AD calculated	**Visual analysis** • high frequency of typical pattern (bilateral temporoparietal and optional frontal hypometabolism) **Metabolic ratio analysis** • AD metabolic ratios significantly lower than controls • differences among ratio means at centers not significant • ratio increased significantly with age, but centers did not differ after age adjustment of ratios • mean value of ratio close to 1.0 over entire age range in controls **Diagnostic accuracy** • composite metabolic ratio yielded better separation of cases from controls than did ratios of single regions by ROC curve analysis • at cutpoint of 0.921, Se = 94.6% and Sp = 97% (95.8% of subjects correctly classified) **Factors affecting variation among centers** • rate constants used (10% change in constant produced < 1% change in composite ratio) • region size (10% increase in size increased ratio by 1.2%) **Conclusion** A common investigation protocol may yield comparable PET data from different centers in spite of differences between scanners and imaging equipment. **Study design limitations** no definitive diagnosis in any DAT subjects
Kippenhan, et al., 1994 *University of Miami , NIA/NIH*	**Purposes** • to generate recommendations for optimal data representation and analysis in diagnosis of AD • to compare the ability of 2 PET cameras (PETT V and Scanditronix, a higher resolution scanner) to diagnose AD using optimal discriminators and a neural network • to define the most generally applicable metabolic discriminators of AD **Cases** • PETT V: 41 patients with NINCDS-ADRDA probable AD • Scanditronix: 33 patients with NINCDS-ADRDA probable AD **Controls** • PETT V: 50 age-matched normal individuals • Scanditronix: 74 age-matched normal individuals **Methods** • small structures from Scanditronix database combined to obtain regional representations equivalent to those of PETT V data at lobular and lobar levels • classification performance from each database evaluated for lobular and lobar representations for various methods of classification (by ROC analysis) and data processing • classifiers evaluated by cross-validation studies on training and testing sets • neural network training by back-propagation techniques • classification results for neural net compared to results using discriminant analysis • different methods to preprocess data compared	**Classification according to global metabolism** areas under ROC curve: Scanditronix .90, PETT V .60 **Results of optimization experiments** • lobular representation and occipital normalized data resulted in best performance for PETT V • lobular data processed with either simple scaling or normalization **Comparison of neural net and discriminant analysis** • performance approximately equal for Scanditronix lobular data • performance of neural net somewhat higher for PETT V lobular data **Can neural nets identify groups in one database after being trained with sets including subjects from other database?** better performance can be expected by training with lower resolution data (“noisier”) and testing on higher resolution data than the reverse (for normalized data) **Most important and generalizable discriminating profiles learned by neural nets during lobule-level training with both databases** • generally low metabolic values in parietal and temporal areas • higher values in motor-sensory and occipital regions • asymmetry **Posttest probabilities of disease** • classification at point of maximum information on ROC curve for normalized Scanditronix lobular data resulted in posttest probability of 90% (rule in disease) for an abnormal test and 10% (rule out disease) for a negative test • corresponding posttest probabilities for PETT V lobular data were 87% and 24% **Authors’ comment** it should be possible to share metabolic data from different scanners and institutions to develop an extensive knowledge base of metabolic patterns **Study design limitation** no definitive diagnosis in any AD cases

Study	*Subjects/Methods*	*Results/Comments*
Salmon, et al., 1994 *University of Liège, Belgium*	**Purpose** to evaluate the role of visual analysis of PET metabolic patterns in patients referred for differential diagnosis of degenerative dementias **Cases** 65 patients with NINCDS-ADRDA probable AD (5 with a diagnosis of definite AD after histologic examination) **Controls** 64 patients whose final diagnosis was: degenerative dementia atypical for AD (possible AD, 19); Parkinson's disease (13); progressive supranuclear palsy (1); vascular dementia (8); mixed dementia (9); Creutzfeldt-Jacob disease (3); metachromatic leukodystrophy (1); dementia from anoxia (1); primary progressive aphasia (2); normal pressure hydrocephalus (3); depression (4) (7/64 confirmed by histologic diagnosis) **Methods** • PET scans acquired in resting state on plane parallel to IOM line • ROIs and visual analyses performed on 7 planes selected with brain atlas • 9 categories of image patterns for hypometabolism: - bilateral temporo-parietal (with/without frontal) - unilateral temporo-parietal (with/without frontal) - frontal regions bilaterally affected more than temporo-parietal - frontal unilaterally affected more than temporo-parietal - isolated bilateral frontal involvement, sometimes asymmetrical - left perisylvian, sometimes extending to homolateral cortices - diffuse cortical, localized above level of basal ganglia - multiple patchy foci, cortical and subcortical - normal • reader (number not specified) blind to clinical data except for suspicion of dementia	**General findings in probable AD group** • 97% of PET scans abnormal • 2 patients with mild dementia had normal scans (1 showed AD pattern 5 years later) • metabolic pattern in AD is heterogeneous; multiple cut points corresponding to subgroups of the 9 patterns are possible **If first 4 image patterns considered positive for AD** • distinguishing AD from dementia atypical for AD: Se = 94%; *Sp = 79%; *PPV = 94%; *NPV = 79% • distinguishing AD from all controls: *Se = 94%; *Sp = 53%; *PPV = 67%; *NPV = 89% **If bilateral temporo-parietal hypometabolism only considered positive for AD** • distinguishing AD from dementia atypical for AD: Se = 66%; *Sp = 89%; *PPV = 96%; *NPV = 44% • distinguishing AD from all controls: *Se = 66%; *Sp = 54%; *PPV = 68%; *NPV = 52% **Study design limitations/comments** • final diagnosis obtained after unspecified time of follow up in many patients; data used at follow up included PET (i.e., diagnostic standard not applied without knowledge of PET result and possible incorporation bias) • only 19 controls (with possible AD)contributed data to authors' analyses • histologic confirmation of diagnosis in small number of patients • "Results" section difficult to interpret; authors indicate that analyses will be restricted to patients with probable or definite AD (cases) and dementia atypical for AD (19/64 controls) but give diagnostic accuracy figures based on all controls • study has significant value in that it tested PET in a population of patients with readily confused diseases (a common clinical situation)

Study	*Subjects/Methods*	*Results/Comments*
Burdette, et al., 1996 *University of Michigan, Ann Arbor*	**Purpose** to compare diagnostic accuracy of 3D stereotactic surface projection PET images to accuracy of transaxial images using ROC analysis in cases and controls obtained retrospectively from research database **Cases** 39 patients with NINCDS-ADRDA probable AD • 28 questionable/mild dementia • 11 moderate/severe dementia **Controls** 40 patients without dementia • 18 patients with cerebrovascular disease (5 multiple infarctions, 8 cerebrovasculitis with systemic lupus erythematosis, 5 moderate/large vascular distribution infarction) • 22 similar-aged normal individuals from database **Methods** • 2 sets of PET images (ordinary projection and 3D stereotactic surface projection) analyzed qualitatively by 2 expert and 2 novice interpreters who received brief training sessions on day of image analysis • each image set presented to interpreters in different randomized order • images scored: definite AD; probable AD; indeterminate; probably not AD; definitely not AD • interpreters blinded to patient identifiers and clinical information • interpreters' response data analyzed using ROC techniques (area under curve, SD, two-tailed p value for each reader and each type of presentation) • data from questionable/mild dementia (more difficult diagnosis) analyzed separately • Se, Sp calculated using definite and probable scores as positive for AD **Study design limitation** no definitive diagnosis in any AD cases	**Discrimination of AD using ΔZ-score, previous study** (Minoshima, et al., 1995) at Sp = 100% (zero false positives): • parietal (cutpoint ΔZ = .55) Se = 95% • temporal (cutpoint ΔZ = .45) Se = 81% • frontal (cutpoint ΔZ = .56) Se = 59% • unilaterally averaged ΔZ (cutpoint ΔZ = 0.36) Se = 97% • bilaterally averaged parietal-temporal-frontal ΔZ (cutpoint ΔZ = .52) Se = 100% • robust ratio from Herholz, et al. (table entry above, cutpoint = .89) Se = 92% • false negatives were mildly demented patients with unilateral hypometabolism • cerebrovascular disease cases: quantitative indices yielded some false positives, but distributions of metabolic abnormalities were clearly distinguishable from AD on visual inspection **ROC analysis, this study** • diagnostic accuracy improved in all readers with 3D stereotactic projections • no difference between beginner and expert readers with 3D stereotactic projections **Transaxial image display, all readers** • Se = 85% ± 0.06 (95% CI. ± 0.10) • Sp = 88% ± 0.02 (95% CI. ± 0.15) **3D stereotactic surface projection, all readers, all subjects** • Se = 94%± 0.02 (95% CI, ± 0.04) • Sp = 99% ± 0.02 (95% CI, ± 0.03) **All readers, questionable/mild dementia subjects** • transaxial projection: Se = 79% ± 0.06 (95% CI, ± 0.02) • 3D stereotactic projection: Se = 94%± 0.01 (95% CI, ± 0.02)

* = calculated by MDRC Technology Assessment Program from information provided in the article

Abbreviations:
AD, Alzheimer's disease
CI, confidence interval
CT, computed tomography
DAT, dementia of Alzheimer's type
EEG, electroencephalography
GMR, glucose metabolic rate
IOM, inferior orbitomeatal line
MANOVA, multivariate analysis of variance
MID, multi-infarct dementia
MMSE, Mini-Mental State Examination
MRI, magnetic resonance imaging
NIA, National Institute on Aging
NIH, National Institutes of Health
NIMH, National Institute of Mental Health
NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association
NPV, negative predictive value
PPV, positive predictive value
ROC, receiver operating characteristic
ROI, region of interest
Se, sensitivity
Sp, specificity

Table 5 Diagnostic accuracy efficacy of neuroimaging alternatives to FDG PET for Alzheimer's disease
Cross sectional studies with controls comparing PET to alternative diagnostic imaging tests using clinical criteria as the diagnostic standard

Notes: *Studies in this table were identified by searches of MEDLINE files for the years 1991 to 1996, using the terms "Alzheimer's disease" and "diagnosis". These studies directly compare other neuroimaging technologies with PET.*

All of the studies used cross sectional designs with controls and appeared to adequately match cases and controls for critical demographic factors.

Study	*Subjects/Methods*	*Results/Comments*
Fazekas, et al., 1989 *University of Pennsylvania*	**Purpose: PET vs CT vs MRI** to describe the type and frequency of brain abnormalities detected by CT, MRI, and PET in DAT and normal aging *information provided allowed calculation of diagnostic characteristics of each test* **AD cases** 30 DAT (DSM-III) • 24 "probable" and 6 "possible" using NINCDS-ADRDA • 14 with mild to moderate DAT according to MMSE, 16 with moderate to severe **Controls** 25 elderly individuals without evidence of dementia, and with medical findings comparable to those in DAT group **Methods** • 28 DAT and 25 controls had CT • 23 DAT and 10 controls had MRI • 30 DAT and 25 controls had FDG PET • for each imaging modality the scans from DAT and control subjects were randomly mixed and interpreted separately by a neuroradiologist (CT and MRI) and a nuclear medicine specialist (PET), without information on the age, sex, or clinical condition of patient • extent of cortical and ventricular atrophy (CT and MRI) and severity of metabolic abnormalities (PET) rated as absent, mild, moderate, or severe	**CT** • cortical atrophy: *Se = 86%; *Sp = 28%; *PPV = 57%; *NPV = 64% (mild, moderate, severe atrophy grouped as abnormal) • ventricular atrophy: *Se = 79%; *Sp = 72%; *PPV = 76%; *NPV = 75% (mild, moderate, severe atrophy grouped as abnormal) • higher grades of cortical and ventricular atrophy found in DAT than in controls and differences in mean rating between DAT and controls was significant ($p < .001$), but considerable overlap in atrophy scores **MRI** *(text and tables present different counts for DAT patients who received MRI; table number used in calculations below)* • cortical atrophy: *Se = 92%; *Sp = 10%; *PPV = 55%; *NPV = 50% (mild, moderate, severe atrophy grouped as abnormal) • ventricular atrophy: *Se = 92%; *Sp = 60%; *PPV = 73%; *NPV = 86% (mild, moderate, severe atrophy grouped as abnormal) • periventricular and/or white matter lesions: *Se = 83%; *Sp = 40%; *PPV = 63%; *NPV = 67% **PET** • *Se = 97%; *Sp = 84%; *PPV = 89%; *NPV = 95% (mild, moderate, severe hypometabolism grouped as abnormal) • abnormalities predominately focal in early DAT, diffuse hypometabolism in more advanced DAT • using visual criteria, the majority of focal metabolic abnormalities could not be explained on the basis of cortical atrophy alone; metabolic dysfunction may precede anatomic changes **Study design limitations** • protocol did not provide for image interpretation by ≥ 2 observers • no definitive diagnosis in any DAT subjects

Study	*Subjects/Methods*	*Results/Comments*
Mielke, et al., 1994 *Max Planck Institut, Germany*	**Purpose: PET vs SPECT** to define the relative ability of HMPAO SPECT and FDG PET to distinguish AD, vascular dementia (VD), and controls **AD cases** 20 patients with NINCDS-ADRDA probable AD **VD controls** 12 patients selected by modified Hachinski scores and NINDS-AIREN criteria **Normal controls** 13 normal subjects with no clinical evidence of cognitive deficits or neurological disease who were part of larger sample with subjective memory impairment **Methods** • patients received SPECT and PET on same day • SPECT and PET images coregistered and standardized ROIs generated • relative regional HMPAO uptake used to assess regional perfusion differences • relative GMR calculated from PET studies • functional pattern typical of AD by SPECT and PET used to calculate ratio of average perfusion or metabolism in affected areas divided by unaffected areas • ROC analysis performed	**General findings** • metabolism ratios in normals significantly related to age, and metabolic differences between normal and AD less obvious in old age • perfusion and metabolism ratios significantly lower in AD than in VD and controls • no significant differences between perfusion ratio and severity of dementia or age **ROC analysis** • for discrimination between AD and controls PET had marginally significant ($p = .05$) advantage (PET Se = 80% at Sp = 100%; SPECT Se = 80% at Sp = 65%) • PET false negatives all in marginally demented patients • SPECT false negatives scattered across range of dementia severity • for differential diagnosis of AD versus VD, PET was superior to SPECT **Conclusions** • both PET and SPECT can distinguish AD from controls • PET is superior in differentiating AD from VD **Study design limitations** • no definitive diagnosis in any DAT subjects

Abbreviations:
AD, Alzheimer's disease
CT, computed tomography
HMPAO, hexamethylpropylene amine oxime
NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association
NINDS-AIREN,
OM, orbitomeatal
ROC, receiver operating characteristic
ROI, region of interest
Se, sensitivity
Sp, specificity
SPECT, single photon emission tomography
VD, vascular dementia

Table 6 Study design models: Diagnostic thinking efficacy of alternatives to FDG PET for Alzheimer's disease

Notes: *The studies tabulated below were identified by searches of MEDLINE files for the years 1991 to 1996, using the terms "Alzheimer's disease" and "diagnosis".*

Van Gool, et al., analyzed two ongoing cohort studies in the Netherlands to estimate the diagnostic accuracy of SPECT in elderly patients presenting for an initial evaluation for mild dementia, and to determine the incremental contribution of SPECT after a thorough clinical and laboratory examination. However, this study did not follow patients to death and autopsy.

The Oxford Project to Investigate Memory and Aging (Jobst, et al.) used that project's cohorts of patients with dementia and age-matched controls; analyses are based on subjects who were followed to death and autopsy. These studies are classified as "diagnostic thinking efficacy" studies because they are presented in a form that allows estimation of the risk of AD for an individual using age-specific prevalence data and the likelihood ratio from that individual's CT.

Study	*Subjects/Methods*	*Results/Comments*
Van Gool, et al., 1995 *Academic Medical Center, Amsterdam, The Netherlands*	**Purpose** to conduct a study to address methodologic deficiencies of existing SPECT studies: • definition of incremental value of SPECT after careful clinical examination • spectrum bias in studies including relatively young patients and patients with advanced disease • diagnostic utility of SPECT in patients representing diagnostic challenge (mildly affected elderly) **Study design** cross sectional with controls **Cases** 110 patients > 65 year referred for first evaluation of dementia **Controls** 18 subjects recruited from prospective community-based study of mental functioning in elderly (65-85 years); controls had suboptimal cognitive scores **Methods** • initial clinical diagnosis using CAMDEX-N interview schedule, with specification of whether SPECT expected to contribute to diagnostic certainty by both individual neurologist and consensus panel • lab, CT, SPECT temporoparietal perfusion data then used with DSM III-R and NINCDS-ADRDA criteria for final diagnosis • all ancillary tests (lab and imaging) scored re contribution to change from initial to final diagnosis • diagnostic classification reconsidered after 6 months, FU to 2 years in some patients • SPECT images scored by consensus of 2 of 3 neurologists blinded to clinical findings (semiquantitative analysis) • Se of SPECT calculated for multiple perfusion value cut points • Sp of SPECT calculated using images from non-demented controls to avoid potential contribution of AD encephalopathy to other primary diagnoses • ROC analyses conducted • a priori requirement that a claim of substantial contribution of SPECT to diagnostic process would be validated if proportion of patients whose diagnosis changed ≤ 20%	**Final diagnoses** • 68 probable AD according to NINCDS-ADRDA criteria • 42 other (multi infarct dementia, unspecified dementia, mixed dementia) **Operating characteristics of SPECT** at temporoparietal perfusion cut point of 0.79 • non demented controls, Sp = 89% • all probable AD, Se = 43% • probable AD < 80 years, Se = 56% • probable AD > 80 years, Se = 29% **Contribution of SPECT to diagnosis** • before imaging, SPECT was expected to contribute to diagnostic certainty in 26% of patients • actual contribution of SPECT to 8% of final diagnoses (5 DAT, 3 mixed dementia, 1 rule out mixed dementia) **Authors' comments** • routine SPECT has limited value in evaluating elderly demented patients • disagreement with other published results attributed to selection bias in other studies (relatively young patients or those with advanced disease, or highly selected healthy controls)

Study	*Subjects/Methods*	*Results/Comments*
Jobst, et al., 1992a 1992b 1994 *Oxford University, UK*	**Purpose** to develop simple, clinically applicable diagnostic measures for AD **Study design** cohorts with and without DAT followed to autopsy **Cases** 45 cases; definitive postmortem diagnosis of AD (using pathologic criteria of Khachaturian) **Controls** •16 with other causes of dementia (documented by postmortem histopathology) • 8 with no dementia in life and no postmortem CNS pathology • 84 living without evidence of cognitive decline **General methods** subjects with and without dementia had detailed, repeated annual assessments (full neuropsychological, psychiatric, physical and radiological screening) until death, when autopsy was carried out **CT methods** quantitative evaluation of atrophy performed from temporal lobe-oriented CT acquired along long axis of medial temporal lobe: • linear measurement of narrowest thickness of medial temporal lobe on right or left side at level of brain stem between its anterior and posterior margins • interrater reliability tested by comparing measurements of 2 observers, blind to diagnosis, on scans from 127 subjects (mean difference of 0.15, good agreement) **SPECT methods** scans assessed semiquantitatively and by consensus • high interrater reliability • perfusion scans graded from 0 (no deficit) to 3 (severe deficit breaching cortical rim)	**CT** at cut point of < 0.79 multiple of median (< 5th percentile for age of controls) = AD (5% false positives): Se = 94%; Sp = 93.5% • measurement falls below fifth percentile for age in confirmed AD at least 4 years before death and certainly prior to onset of severe dementia • results permit estimation of risk for AD for individual using age-specific prevalence data and likelihood ratio from individual's value for minimum thickness of medial temporal lobe (LR = ratio of height of gaussian curve for AD to height of curve for controls at a patient's value of the minimum thickness of the temporal lobe) **SPECT** Grade ≥ 2 perfusion deficit in temporoparietal cortex = AD: Se = 96%; Sp = 89% **CT + SPECT** using < 5th percentile for age medial temporal lobe measurement on CT and grade ≥ 2 perfusion deficit in temporoparietal cortex on SPECT = AD (3% false positives): Se = 90%; Sp = 97% **Authors' conclusions** • cognitive evaluation plus CT plus SPECT decreased average false positive rate of 25% using clinical criteria alone to less than 5% • Main immediate value of findings is to identify groups at high enough risk of AD to justify recruitment into clinical trials of potential new therapies

Abbreviations: AD, Alzheimer's disease
CT, computed tomography
Se, sensitivity
Sp, specificity
SPECT, single photon emission tomography

VI. REFERENCES: Background and diagnostic accuracy/diagnostic thinking efficacy studies

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VIII. REFERENCES: Excluded studies

Exclusion criteria were:

- number of DAT cases < 12
- duplicated or superseded by subsequent study from the same institution
- behavioral or cognitive activation rather than resting FDG PET
- radiopharmaceutical other than FDG
- case series (without controls)
- diagnostic accuracy efficacy study where PET data were interpreted visually but blinding was not noted
- DAT diagnostic criteria not specified
- insufficient information to judge comparability of case and control groups, details of imaging protocol, whether visual or quantitative analysis of PET data used, or type of PET data analysis used

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